

Amendments to the Specification

In the Specification:

Please insert the following paragraph before paragraph [0001]:

CROSS -REFERENCE TO RELATED APPLICATIONS

This application is a national phase entry of International Appl. No. PCT/US2003/038949, filed December 10, 2003, which published under PCT Article 21(2) in English, said PCT/US2003/038949 claims the benefit of U.S. Provisional Appl. No. 60/432,017, filed December 10, 2002; each of said applications is herein incorporated by reference.

Please replace paragraph [0102] with the following paragraph:

The HTL peptide may comprise a "loosely HLA-restricted" or "promiscuous" sequence. Examples of amino acid sequences that are promiscuous include sequences from antigens such as tetanus toxoid at positions 830-843 (QYIKANSKFIGITE; SEQ ID NO: 26 [[627]]), Plasmodium falciparum CS protein at positions 378-398 (DIEKKIAKMEKASSVFNVVNS; SEQ ID NO: 27 [[628]]), and Streptococcus 18kD protein at positions 116-131 (GAVDSILGGVATYGAA; SEQ ID NO: 28 [[629]]). Other examples include peptides bearing a DR 1-4-7 supermotif, or either of the DR3 motifs.

Please replace paragraph [0103] with the following paragraph:

The HTL peptide may comprise a synthetic peptide such as a Pan-DR-binding epitope (*e.g.*, a PADRE[®] peptide, Epimmune Inc., San Diego, CA, described, for example, in U.S. Patent Number 5,736,142), for example, having the formula aKXVAAZTLKAAa (SEQ ID NO:29), where “X” is either cyclohexylalanine, phenylalanine, or tyrosine; “Z” is either tryptophan, tyrosine, histidine or asparagine; and “a” is either D-alanine or L-alanine (~~SEQ ID NO: 746~~). Certain pan-DR binding epitopes comprise all “L” natural amino acids; these molecules can be provided as peptides or in the form of nucleic acids that encode the peptide. See also, U.S. Patent Nos. 5,679,640 and 6,413,935.

Please replace paragraph [0312] with the following paragraph:

A particularly preferred PADRE[®] molecule is a synthetic peptide, aKXVAAWTLKAAa (SEQ ID NO:29) (a = D-alanine, X = cyclohexylalanine), containing non-natural amino acids, specifically engineered to maximize both HLA-DR binding capacity and induction of T cell immune responses.

Please replace paragraph [0313] with the following paragraph:

Alternative preferred PADRE[®] molecules are the peptides, aKFVAAWTLKAAa (SEQ ID NO:29), aKYVAAWTLKAAa (SEQ ID NO:29), aKFVAAAYTLKAAa (SEQ ID NO:29), aKXVAAAYTLKAAa (SEQ ID NO:29), aKYVAAAYTLKAAa (SEQ ID

NO:29), aKFVAAHTLKAAa (SEQ ID NO:29), aKXVAAHTLKAAa (SEQ ID NO:29), aKYVAAHTLKAAa (SEQ ID NO:29), aKFVAANTLKAAa (SEQ ID NO:29), aKXVAANTLKAAa (SEQ ID NO:29), aKYVAANTLKAAa (SEQ ID NO:29), AKXVAAWTLKAAA (SEQ ID NO:30), AKFVAAWTLKAAA (SEQ ID NO:31), AKYVAAWTLKAAA (SEQ ID NO:32), AKFVAAYTLKAAA (SEQ ID NO:33), AKXVAAYTLKAAA (SEQ ID NO:34), AKYVAAYTLKAAA (SEQ ID NO:35), AKFVAAHTLKAAA (SEQ ID NO:36), aKXVAAHTLKAAA (SEQ ID NO:37), aKYVAAHTLKAAA (SEQ ID NO:38), aKFVAANTLKAAA (SEQ ID NO:39), aKXVAANTLKAAA (SEQ ID NO:40), aKYVAANTLKAAA (SEQ ID NO:41) (a = D-alanine, X = cyclohexylalanine).

Please replace paragraph [0314] with the following paragraph:

In a presently preferred embodiment, the PADRE[®] peptide is amidated. For example, a particularly preferred amidated embodiment of a PADRE[®] molecule is conventionally written aKXVAAWTLKAAa-NH₂ (SEQ ID NO:29).

Please replace paragraph [0316] with the following paragraph:

PADRE[®] has been specifically engineered for optimal immunogenicity for human T cells. Representative data from in vitro primary immunizations of normal human T cells with TT 830-843 antigen and the PADRE[®] molecule aKXVAAWTLKAAa-NH₂ (SEQ ID NO:29) are shown in Figure 1. Peripheral blood

mononuclear cells (PBMC) from three normal donors were stimulated with the peptides in vitro. Following the third round of stimulation, it was observed that PADRE[®] generated significant primary T cell responses for all three donors as measured in a standard T cell proliferation assay. With the PADRE[®] peptide, the 10,000 cpm proliferation level was generally reached with 10 to 100 ng/ml of antigen. In contrast, TT 830-843 antigen generated responses for only 2 out of 3 of the individuals tested. Responses approaching the 10,000 cpm range were reached with about 10,000 ng/ml of antigen. In this respect, it was noted that PADRE[®] was, on a molar basis, about 100-fold more potent than TT 830-843 antigen for activation of T cell responses.

Please replace paragraph [0317] with the following paragraph:

Early data from a phase I/II investigator-sponsored trial, conducted at the University of Leiden (C.J.M. Melief), support the principle that the PADRE[®] molecule aKXVAAWTLKAAa (SEQ ID NO:29), possibly the amidated aKXVAAWTLKAAa-NH₂ (SEQ ID NO:29), is highly immunogenic in humans (Ressing *et al.*, *Detection of immune responses to helper peptide, but not to viral CTL epitopes, following peptide vaccination of immunocompromised patients with recurrent cervical carcinoma*. (J. Immunother. 23(2):255-66 (2000)). In this trial, a PADRE[®] molecule was co-emulsified with various human papilloma virus (HPV)-derived CTL epitopes and was injected into patients with recurrent or residual cervical carcinoma. However, because of the late stage of carcinoma with the study patients, it was expected that these patients were immunocompromised. The patients' immunocompromised status was demonstrated by

their low frequency of influenza virus-specific CTL, reduced levels of CD3 expression, and low incidence of proliferative recall responses after *in vitro* stimulation with conventional antigens. Thus, no efficacy was anticipated in the University of Leiden trial, rather the goal of that trial was essentially to evaluate safety. Safety was, in fact, demonstrated. In addition to a favorable safety profile, PADRE® T cell reactivity was detected in four of 12 patients (Figure 2) in spite of the reduced immune competence of these patients.

Please replace paragraph [0351] with the following paragraph:

Two peptides that stimulate HLA class II are also used in accordance with the invention. For instance, a pan-DR-binding epitope peptide having the formula: aKXVAAZTLKAAa, where “X” is either cyclohexylalanine, phenylalanine, or tyrosine; “Z” is either tryptophan, tyrosine, histidine or asparagine; and “a” is either D-alanine or L-alanine (SEQ ID NO:29), has been found to bind to most HLA-DR alleles, and to stimulate the response of T helper lymphocytes from most individuals, regardless of their HLA type. Two particularly preferred PADRE® molecules are the peptides, aKFVAAZTLKAAa-NH₂ (SEQ ID NO:29) and aKXVAAHTLKAAa-NH₂ (SEQ ID NO:29) (a = D-alanine, X = cyclohexylalanine), the latter containing a non-natural amino acid, specifically engineered to maximize both HLA-DR binding capacity and induction of T cell immune responses.

Please replace pending page 172 of the specification with attached page 172.

Please replace pending page 194 of the specification with attached page 194.

Please replace pending page 219 of the specification with attached page 219.

Please cancel the existing Sequence Listing for the above-identified application, replace it with the substitute Sequence Listing appended hereto, and insert the same at the end of the application.

Table 4

MOTIFS	POSITION					
	<u>1° anchor 1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>1° anchor 6</u>
DR4 preferred	F, M, Y, L, I, V, W	M	T		I	V, S, T, C, P, A, L, I, M
deleterious				W		R, W, D, E
DR1 preferred	M, F, L, I, V, W, Y			P, A, M, Q		V, M, A, T, S, P, L, I, C
deleterious		C	C, H	F, D	C, W, D	G, D, E, D
DR7 preferred	M, F, L, I, V, W, Y	M	W	A		L, V, M, S, A, C, T, P, L
deleterious		C		G		G, R, D, N, G
DR Supermotif	M, F, L, I, V, W, Y					V, M, S, T, A, C, P, L, I
DR3 MOTIFS	<u>1° anchor 1</u>	<u>2</u>	<u>3</u>	<u>1° anchor 4</u>	<u>5</u>	<u>1° anchor 6</u>
motif a preferred	L, I, V, M, F, Y			D		
motif b preferred	L, I, V, M, F, A, Y			D, N, Q, E, S, T		K, R, H

Italicized residues indicate less preferred or "tolerated" residues.

Table 18b. Her2/neu-derived A1 binders

SEQ ID NO	AA	Sequence	Source	A*0101 nM
185	9	VMAGVGSPY	Her2/neu.773	625
186	9	VMDGVGSPY	Her2/neu.773.D3	40
187	10	CMQIAKGMSY	Her2/neu.826	83
188	10	CTQIAKGMSY	Her2/neu.826.T2	19
189	9	LLDIDETAY	Her2/neu.869	3.3
190	9	LTDIDETAY	Her2/neu.869.T2	5.7
191	10	FTHQSDVWSY	Her2/neu.899	9.3
192	10	FTDQSDVWSY	Her2/neu.899.D3	0.60
193	10	PASPLDSTFY	Her2/neu.996	1667
194	10	PADPLDSTFY	Her2/neu.996.D3	19
195	9	ASPLDSTFY	Her2/neu.997	862
196	9	ATPLDSTFY	Her2/neu.997.T2	36
197	10	MGDLVDAEEY	Her2/neu.1014	2083
198	10	MTDLVDAEEY	Her2/neu.1014.T2	2.3
199	9	LTCSPQPEY	Her2/neu.1131	192
200	9	LTDSPQPEY	Her2/neu.1131.D3	32
201	10	FSPAFDNLYY	Her2/neu.1213	4.5
<u>202</u>	212	FTPFDNLYY	Her2/neu.1213.T2	0.80
203	9	FSPAFDNLY	Her2/neu.1213	581
204	9	FTPFDNLY	Her2/neu.1213.T2	7.8
205	9	SPAFDNLYY	Her2/neu.1214	NT
206	9	SPDFDNLYY	Her2/neu.1214.D3	74
207	10	GTPTAENPEY	Her2/neu.1239	397
208	10	GTDTAENPEY	Her2/neu.1239.D3	26

-- indicates binding affinity =10,000nM.

Table 31. Hepatitis B Virus Core Protein (~~SEQ ID NO: 754~~) (SEQ ID NO: 746)

MQLFHLCCLIISCSCPTVQASKLCLGWLWGMDIDPYKEFGATVELLSFLPSDFFPSV
RDLLDTASALYREALSPEHCSPHHTALRQAILCWGELMTLATWVGVNLEDPASR
DLVVS YVNTNMGLKFRQLLWFHISCLTFGRETVIEYLVSGVWIRTPPAYRPPNAPIL
STLPETTVVRRRGRSPRRRTSPRRRRRSQSPRRRRRSQSRESQC

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